Am. J. Hum. Genet. 47:603–605, 1990

Invited Editorial: Carrier Screening for Cystic Fibrosis

Arthur L. Beaudet

Howard Hughes Medical Institute and Institute for Molecular Genetics, Baylor College of Medicine, Houston

Statements from The American Society of Human Genetics and from an NIH workshop have urged that population-based carrier testing for cystic fibrosis (CF) not be implemented immediately (Caskey et al. 1990; Workshop on Population Screening for the Cystic Fibrosis Gene 1990). Others have urged that carrier testing be more widely and immediately available (Goodfellow 1989; Brock 1990; Schulman et al. 1990). What are the arguments for these differing views? Are different countries following opposite courses? How should these decisions be made? Numerous opinions and comments are already published, most of which are referenced in a recent review (Wilfond and Fost 1990).

How does the current status of the laboratory test bear on the debate regarding CF screening? Because mutation analysis today detects only a fraction of all carriers, certain difficulties arise, as depicted in table 1. At rates of mutation detection of interest (75%–95%), a large fraction of couples (1/12–15) are left with increased risks (1/400–2,000) of bearing a child having CF. Microvillar intestinal enzyme analysis and use of linkage disequilibrium data (Beaudet et al. 1989) will not satisfactorily resolve the risks for these families. Recognizing important ethnic and geographical differences, the present discussion will focus on numbers relevant to a North American Caucasian population of mixed European ancestry. On the basis of our unpublished experience analyzing mutations identified through the CF Genetic Analysis Consortium, it appears practical at the present time to test for four to seven mutations to detect about 85% of carriers. This would mean that 72% (85% × 85%) of couples at risk would be fully identified, i.e., the sensitivity for detection of couples at risk would be 72%. For the 1/12–15 couples in which one partner has a negative test and one has a positive test, the risk for CF in their first offspring would be about 1/600. As the ability to detect mutations increases, two benefits occur, as shown in table 1. First, a higher percentage of at-risk couples is identified. Second, the level of risk for the 1/12–15 couples in which one partner has a positive test decreases and approaches the starting risk of 1/2,500 once 95%–96% detection of mutations is possible. On the optimistic side, it seems possible that 90% detection will be attainable by testing 8–12 mutations. On the pessimistic side, it appears that more than 97% detection will be virtually impossible unless one is able to test for 30–40 or more mutations. Since cost is an important factor, perhaps testing to achieve 90% detection for less than $150 is an immediate goal, while testing to achieve 95% detection for less than $100 would be a challenging goal for a year or two from now.

What are the potential benefits of screening for CF carriers? At the present time, there is only a single major benefit, which is the option to make more informed reproductive decisions with the knowledge that some proportion of families would choose to prevent the disease. Although some would argue that the success of the program should be judged solely by the effectiveness of the educational program (i.e., whether screenees understood the information), it is clear that prevention of CF is also, at some level, a measure of a screening program, since few would advocate expending the substantial resources involved if very few families wish to avoid the disease. Reduction in the incidence of CF is likely to vary substantially from country to country—and from region to region within the United States—as well as with other socioeconomic, cultural, and educational variables. Some geneticists have yearned for the day when carrier testing for CF might join rubella vaccine, Rh immunization, and newborn screening for phenylketonuria as a success story in prevention or treatment of illness. It will not be so simple. Any prevention program which depends on alteration of reproductive plans and/or selective abortion cannot be viewed as simply as can a vaccine or a beneficial diet or drug, particularly in light of the complex phenotypic and prognostic variables for CF. The benefits of carrier testing are

Received July 24, 1990.

Address for correspondence and reprints: Arthur L. Beaudet, M.D., Institute for Molecular Genetics, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030.

0002-9297/90/4704-0002$02.00

Table 1

Effect of Rate of Mutation Detection on Carrier Testing

% Mutation Detection	Risk of CF if One Parent Is Carrier and Other Has Negative Test	% of At-Risk Couples Detected
75	1/396	56
85	1/661	72
95	1/1,964	90
99	1/9,814	98

NOTE.—See Lemna et al. (1990) or ten Kate (1990) for calculations.

already substantial and would be increased moderately by an improved test.

What are the potential harms and risks of carrier testing? The drawbacks of carrier testing have been emphasized (Billings 1990; Colten 1990) and were reviewed recently in greater detail than space permits here (Wilfond and Fost 1990). One problem is anxiety regarding the potential birth of a child with CF to couples who are not actually at risk. Currently this is a major problem for 1/12–15 couples tested, because one partner is a definite carrier while the other has a negative test. These couples have an increased risk (1/400–600) for having an affected child, as discussed above, and improved mutation detection would substantially reduce the risk for most of these couples. Another problem, misunderstanding of test results, is tied to the need for educational programs and trained counselors. The education complexities would be ameliorated but by no means eliminated by an improved test.

Many other harms and risks of CF carrier testing were reviewed by Wilfond and Fost (1990), and most are not substantially impacted by improving the test. Stigmatization of carriers includes societal and self-stigmatization. In the health-care system in the United States, discrimination against carriers and carrier couples is most worrisome with regard to health insurance and employment; employers may discriminate against employees whose dependents incur high medical costs. There may be both social pressure not to terminate pregnancies and conflicting social pressure not to bear affected offspring. Recommendations to test relatives of known carriers may increase the efficiency of a program but may reveal instances of nonpaternity. There are valid differences of opinion regarding where good medical and genetic health care ends and where inappropriate eugenics begins. The natural history of CF is a complex spectrum to explain to families who have not experienced the disease, and the appropriate balance of reality regarding the burden versus optimism for therapeutic advances is difficult to achieve in a counseling session. Finally, in light of all the other needs of society, are the financial burdens of carrier testing manageable or acceptable? Although it has been estimated that prevention of a single case of CF might cost as much as $1–$2.2 million (Wilfond and Fost 1990), this number would be substantially lower if one assumed that more than 40% of couples would choose to avoid the disease, if most couples were assumed to have more than one pregnancy, and if relatives of carriers preferentially sought carrier testing. In addition, the cost to identify an at-risk couple in a second generation would be reduced by about 13-fold if testing were offered only to offspring of known carriers.

Given these considerations, how does one decide whether to offer testing on a widespread basis? In countries with national health-care systems, presumably committees of experts with extensive societal participation will set policy. The benefits should be compared with the burdens and risks. The recommendations of the U.S. National Academy of Sciences have long provided good guidelines for these decisions (Committee on Inborn Errors of Metabolism 1975). The Cystic Fibrosis Research Trust in the United Kingdom accepted applications for pilot programs in March of 1990, and these studies should provide additional data for decision making. To my knowledge, no country or health-care system has adopted population-based screening as a policy yet, but this appears more imminent in some European countries than in the United States. There will continue to be strong differences of opinion regarding carrier testing, because of differences in attitudes regarding multiple aspects of the perceived benefits and

risks. This coordinated national approach would seem to be the preferable decision-making process.

In the United States, factors determining implementation of carrier testing are likely to differ substantially because of differences in the health-care system, in the medicolegal climate, in the commercial implications, and in societal attitudes. While there is agreement that pilot studies, quality assurance, and educational programs are essential, there are no specific announced funding mechanisms for any of these activities at the time of this writing. The statement of the NIH workshop forms some part of a decision-making process in the United States (Workshop on Population Screening for the Cystic Fibrosis Gene 1990) and, combined with the recommendations of the National Academy of Sciences, should provide guidelines for groups wishing to perform testing. The National Academy of Sciences recommendations strongly emphasize that genetic screening requires, among other features, public benefit and acceptance, public education, counseling resources, and investigative pretest of the program (Committee on Inborn Errors of Metabolism 1975). Additional statements may be useful in the future. These should blunt inappropriate commercial or medicolegal pressures. In practice, it seems likely that carrier screening in the United States will parallel the experience of maternal serum alpha-fetoprotein (MSAFP) screening programs. There is likely to be a progressive growth of the activity, perhaps limited primarily by the willingness of families and providers to pay for the test and by the level of interest in the population. As is the case for MSAFP, some will view the programs as successful and others will cite them as disastrous. In my opinion, these different perceptions derive more from different moral and ethical views than from any medical or scientific facts. Apart from eugenic concerns, the major ethical issue appears to be whether one is willing to accept any harm from the screening program—even if such harm is small by comparison with the benefits—and particularly if it is virtually impossible to educate potential screenees perfectly regarding every aspect of the potential risks. I believe it is inevitable that the screening option will be offered more routinely once the mutation detection rate reaches 90%–95%. It is the responsibility of the genetics community to do everything in its power to see that, if widespread screening is offered, it is conducted as optimally as is realistically possible. The harm which will come from "premature" screening without ideal pilot-program data must be balanced against the harm of not presenting the screening option to at-risk couples. Geneticists probably will influence—if not determine—the course of events in their communities during the next 1–5 years. This participation in setting the standard of care will be a major part of the decision-making process in the United States.

Looking ahead a generation, I believe these options may be moot. One will either be or not be the offspring of a known CF carrier. It is likely that parents will have considerable other genotypic data regarding their disease risks, as other testing becomes "piggybacked" onto CF testing using automated methods. It is to be hoped that CF carrier testing will become a vehicle for greatly increasing the population's educational level regarding the influence of genetics on both health and disease. It is difficult to predict the outcome of the competition between improved treatment for CF and prevention through altered reproduction, but both promise to decrease the burden of the disease in society.

References

Beaudet AL, Feldman GL, Fernbach SD, Buffone GJ, O'Brien WE (1989) Linkage disequilibrium, cystic fibrosis, and genetic counseling. Am J Hum Genet 44:319–326

Billings PR (1990) Mutation analysis in cystic fibrosis. N Engl J Med 323:62

Brock D (1990) Population screening for cystic fibrosis. Am J Hum Genet 47:164–165

Caskey CT, Kaback MM, Beaudet AL (1990) The American Society of Human Genetics statement on cystic fibrosis screening. Am J Hum Genet 46:393

Colten HR (1990) Screening for cystic fibrosis. N Engl J Med 322:328–329

Committee on Inborn Errors of Metabolism (1975) Genetic screening: programs, principles, and research. National Academy of Sciences, Washington, DC

Goodfellow PN (1989) Steady steps lead to the gene. Nature 341:102–103

Schulman JD, Maddalena A, Black SH, Bick DP (1990) Screening for cystic fibrosis carriers. Am J Hum Genet 47:740

ten Kate LP (1990) Carrier screening for cystic fibrosis and other autosomal recessive diseases. Am J Hum Genet 47:259–261

Wilfond BS, Fost N (1990) The cystic fibrosis gene: medical and social implications for heterozygote detection. JAMA 263:2777–2783

Workshop on Population Screening for the Cystic Fibrosis Gene (1990) Statement from the National Institutes of Health Workshop on Population Screening for the Cystic Fibrosis Gene. N Engl J Med 323:70–71